REMARKS

Applicants respectfully request entry of the above amendments to the specification and claims. Applicants acknowledge the entry of the previously filed amendments to the drawings noted by the Examiner in the Advisory Action mailed on November 4, 2003. The specification has been amended to reflect this amendment to the drawings. No new matter is added by way of the amendments to the specification or claims.

The amendment to claim 1 finds support in the specification, for example, at page 6, lines 13-14; Examples 2 and 3, which demonstrate control of proliferation and migration of smooth muscle cells *in vitro*, and elsewhere in the specification and claims as originally filed. Claims 1-3, 5-14, 23-31, and 37-45 were pending in the application. With entry of the requested amendment, claims 1-3, 5-7, 9-11, and 23-27 are pending.

Solely to expedite prosecution of the pending application to issue, claim 1 has been amended to refer to *in vitro* application; claims referring to *in vivo* administration have been canceled by the amendment. Thus, with the amendment, all claims refer to methods for controlling excessive proliferation or migration of smooth muscle cells *in vitro*.

Claims 1-3, 5-14, 23-31 and 37-45 stand rejected under 35 USC § 112, first paragraph, as allegedly not enabling; claims 1-3, 5-14, 23-31 and 37-45 stand rejected under 35 USC § 103(a) as allegedly obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681 and further in view of a known fact. The drawings stand objected to as failing to comply with 27 C.F.R. § 1.84.

Applicants respectfully traverse the rejections.

The Rejections under. § 112 ¶1

Claims 1-3, 5-14, 23-31 and 37-45 were rejected under 35 USC § 112, first paragraph, as allegedly not enabling. However, applicants respectfully note that the Examiner states that claims 1-3, 5-14, 23-31 and 37-45 are "enabling for a method of partially inhibiting proliferation or migration of smooth muscle cells in cell culture, comprising administering an effective amount of an antibody to native ErbB4 receptor" (page 3, paragraph 4, lines 2-5 of the paragraph). Applicants respectfully note that claim 1 has been amended to recite a "method for controlling excessive proliferation or migration of smooth muscle cells *in vitro* comprising treating said smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2."

Applicants further note that the word "control" is defined in the specification (page 13, lines 10-14): "the term 'control' and grammatical variants thereof, as used to refer to the prevention, partial or complete inhibition, reduction, delay, or slowing down of an unwanted event, e.g., physiological condition, such as the excessive proliferation and/or migration of smooth muscle cells and/or other cell types, e.g., endothelial cells." Applicants note that the specification thus clearly states that controlling excessive proliferation or migration of smooth muscle cells includes partial inhibition, or complete inhibition, or reduction, or delay, or slowing down of excessive proliferation or migration of smooth muscle cells.

Thus the claimed methods for controlling excessive proliferation or migration of smooth muscle cells *in vitro* refer to methods for the prevention, partial or complete inhibition, reduction, delay, or slowing down of excessive proliferation or migration of smooth muscle cells *in vitro*. Such control is demonstrated in Examples 2 and 3 and elsewhere in the specification, so as to enable one of ordinary skill in the art to make and use the invention.

Accordingly, applicants respectfully submit that the rejection to claims 1-3, 5-14, 23-31 and 37-45 under 35 USC § 112, first paragraph, as allegedly not enabling is overcome.

The Rejections under U.S.C. § 103(a)

Claims 1-3, 5-14, 23-31 and 37-45 were rejected under 35 USC § 103(a) as obvious over US Patent No. 5,811,098 in view of Krymskaya (1999) or Godowski, WO 99/02681 and further in view of a known fact.

Applicants respectfully submit that the pending claims are not obvious over the cited combination of references.

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that motivation or suggestion to combine the references is lacking, that there would be no reasonable expectation of success based on these references, and that the references cited by the Examiner fail to provide all the elements of the claimed invention. For example, the cited references lack disclosure of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2.

Plowman et al. is presented by the Examiner to show control of excessive proliferation of cancer cells and to present an amino acid sequence of HER 4 receptor said by the Examiner to be identical to SEQ ID NO:2. Krymskaya et al. is presented by

the Examiner to show the presence of ErbB4 receptors on human airway smooth muscle cells; WO 99/02681 is presented by the Examiner to show that ErbB4 receptors are present on smooth muscle cells, and that blocking signal transduction pathway mediated through this receptor can effect mitotic activity in cells expressing these receptors; and the known fact disclosed in the specification at page 5, lines 7-25 is that excessive proliferation of smooth muscle cells is involved with vascular stenosis, restenosis, and hypertension and regulation of proliferation of such cells has potential significance in treating these pathologies. Applicants respectfully note that the present claims, as amended, are directed to controlling excessive proliferation or migration of smooth muscle cells *in vitro*; applicants respectfully submit that considerations of *in vivo* effects are thus moot.

Moreover, even if combined, the cited references fail to make obvious the claimed invention. For example, combination of the cited references lacks elements of the claimed invention. None of the cited references discuss or suggest a method for controlling excessive proliferation or migration of smooth muscle cells *in vitro* by treating smooth muscle cells with an effective amount of an antibody antagonist of a native ErbB4 receptor of SEQ ID NO.: 2. In addition, the cited references lack any teaching that antagonists to ErbB4 receptors would be effective to reduce smooth muscle proliferation (Krymskaya et al. teach that ErbB4 receptors are inactive, WO 99/02681 contains no disclosure regarding antagonizing ErbB4 receptors to reduce smooth muscle cell proliferation). The cited references do not provide any teaching that control of cancer cell proliferation by antibody administration might be relevant to a method for control of smooth muscle proliferation or migration. Accordingly, lacking these elements, lacking any suggestion or motivation to combine to the references to provide the claimed invention, and providing no reasonable expectation of success for such a combination, the combined references fail to make obvious the claimed invention.

As discussed in the previous response, applicants respectfully disagree with the Examiner's suggestion that Krymskaya et al. suggest that the ErbB4 receptor plays "a

pivotal role in the regulation of smooth muscle cells ..." Applicants respectfully direct the Examiner's attention to Krymskaya et al., page L252, column 2, lines 7-9: "Although all EGFR family members are expressed in quiescent HASM [human airway smooth muscle] cells, ErbB-3 and ErbB-4 are functionally inactive." Applicants further note page L248, column 2, lines 37-39: "ErbB-3 and ErbB-4 in EGF-stimulated cells did not appear to be activated." Thus, Krymskaya et al. teach that ErbB4 receptors do NOT play a role in smooth muscle cell proliferation of human airway smooth muscle cells. Krynskaya et al. thus teach that interaction with an ErbB-4 receptor would be ineffective at affecting smooth muscle cell proliferation, teaching away from the claimed invention.

Teaching that ErbB-4 receptors are functionally inactive on the smooth muscle cells investigated, Krymskaya et al. does not provide any motivation to combine with any other reference to control excessive proliferation of smooth muscle cells, or affect stenosis or restenosis, by treatment with an antagonist to an ErbB4 receptor. Krymskaya et al. in combination with the other cited references thus provides no teaching that one could control excessive smooth muscle cell proliferation, by treatment with an antagonist to an ErbB4 receptor of SEQ ID NO:2.

In addition, WO 99/02681 nowhere suggests that antagonists to ErbB4 receptors might be useful to control smooth muscle proliferation. Accordingly, WO 99/02681 provides no teaching that would render obvious the claimed invention, nor any suggestion that it be combined with other references to provide the claimed invention.

Moreover, as stated by the Examiner, US '98 does not provide a method for controlling excessive proliferation or migration of smooth muscle cells. Being directed to cancer cells, US '98 also fails to suggest such a method. Being directed to cancer cells, US '98 also fails to provide any motivation to be combined with any other reference to provide such a method directed to smooth muscle cells.

"Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Applicants respectfully submit that WO 99/02681 provides no suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to provide ErbB-4 antagonists of SEQ ID NO: 2 to control smooth muscle cell proliferation, and that its use in a combination of references to provide such a teaching must be the result of impermissible hindsight. Similarly, US '98 also fails to provide any suggestion or motivation to combine with any other reference or with knowledge available to one of ordinary skill in the art to provide ErbB-4 antagonists of SEQ ID NO: 2 to control smooth muscle cell proliferation.

Lacking any suggestion or motivation to provide methods of controlling excessive proliferation or migration of smooth muscle cells, the cited references fail to provide a reasonable expectation of success of such a combination.

Accordingly, the cited references failing to provide all the elements of the claimed invention, failing to suggest or provide motivation to provide such elements, and failing to provide a reasonable expectation of success for such a combination, Applicants respectfully submit that the rejections of claims 1-3, 4-14, 22-31 and 37-45 under 35 U.S.C. § 103(a) are overcome.

CONCLUSIONS

Applicants believe all rejections to be overcome as discussed above, and respectfully request the entry of the amendments, reconsideration and allowance of all pending claims. All claims being believed to be in *prima facie* condition for allowance, an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing attorney's docket no. **39766-0072 A2**.

Respectfully submitted,

Dated: January 13, 2004 By: _____
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